Will Neurobiology Rise to the Translational Challenges and Opportunities of Late-Life Geriatric Psychiatry?

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Improved care and treatments of subjects suffering from age-related brain illnesses will come through a better understanding of basic biologic mechanisms engaged during both normal and pathologic states. The urgency of this statement is underscored by the rapidly growing aging population and extending longevity, topics often debated in the columns of this journal and summarized by Evans[1] in this issue and by the large gaps in the current knowledge of the biologic bases of aging and of aging of the brain in particular. The premise that the biologic understanding of age- and brain-related mechanisms will lead to strategies and therapies to treat and prevent neuropsychiatric disorders of late life and to promote healthy and successful aging rests on the following tenets. First, complex brain functions and disorders are the expression of deregulated biologic functions that span multiple biologic scales, from genes and cells up to neural networks and behaviors. Second, the complexity of the brain under health and disease conditions can be deconstructed down to biologic levels that are amenable to molecular targeting. Indeed, the field of investigation of the neurobiology of diseases is concerned with cellular and molecular mechanisms of those illnesses and with the identification of targets that can be used to manipulate biologic and functional outcomes. However, current therapeutic agents used in psychiatry originate mostly from the serendipitous discovery of compounds displaying clinical efficacy, as illustrated by antidepressants and neuroleptics for instance, and successes in the rational design of new drugs have been limited to tweaking the chemistry and targets of existing compounds. Indeed, de novo strategies aimed at developing new therapeutics, based on knowledge of deregulated biologic pathways in psychiatric disorders, have been rare and unsuccessful. Therfore, the major challenge of advancing neurobiologic understanding and new drug discovery is not unique to late-life geriatric psychiatry. However, would the added complexity of the multiple brain changes and compounded pathologies that occur with advanced aging put this challenge beyond the reach of systematic neurobiologic investigations?

To begin answering this question, it is worth stepping back and looking at some principles that guide neurobiologic investigations of disease states. The first principle is that of a bottom-up characterization of disease mechanisms from genes, cells, and local circuits, all the way to the expression of behavioral symptom dimensions. This approach often relies on more tractable biologic models (cell-based or animal-based studies) and samples (e.g., postmortem human brain) and contrasts greatly with the clinical characterization of psychiatric disorders, which is based on clusters of symptoms in the absence of underlying biologic knowledge. A second guiding principle is the investigation of biologic changes against the specificities of the "control" groups. Although this principle is self-evident and shared with the field of clinical research, "control"

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http://dx.doi.org/10.1016/j.jagp.2013.02.016

elderly subjects are characterized by multiple brain changes that distinguish them from other adult subjects. Indeed, emerging evidence suggests that normal aging of the brain follows a well-orchestrated and relatively specific set of biologic events.[2,3] Notably, the characterization of these "normal" age-related brain changes is beginning to reveal clues to mechanisms potentially underlying both vulnerability for and resiliency against late-life geriatric disorders. The implication is that the characteristics of aging demonstrated by control elderly subjects may in fact provide unique opportunities, not otherwise available in younger or midlife cohorts, for uncovering mechanisms related to late-life geriatric disorders. Evidence demonstrating lifelong continuous biologic changes in the brain further suggests that findings in geriatric subjects will have implications beyond that population, likely extending to similar disorders earlier in life.[2,3] However, these unique opportunities (i.e., provided by the changing biologic landscape in control aging subjects and for identifying mechanisms related to geriatric psychiatry) are currently untapped or grossly underused.

Here, some of the basic concepts of biologic brain aging are briefly reviewed and findings from articles in this issue are summarized, together providing either frameworks for these neurobiologic endeavors or specific examples. As demonstrated in this issue, the *American Journal of Geriatric Psychiatry* is well positioned to provide a forum to facilitate the translational dialogue between clinical research and biologic mechanisms of age-related disorders, with the goals of exposing clinical researchers to basic concepts and to provide basic scientists with a clinical perspective on the specificities of late-life geriatric psychiatry.

Despite its critical importance to a population growing older, "normal" brain aging and its association with late-life diseases is clearly an understudied area of research. This may be due to the common belief, including from many researchers, that aging may be inescapable and biologically too broad-ranging and nonspecific. However, the identification of single gene mutations affecting aging in multiple model systems from lower organisms to rodents clearly suggests the presence of a genetic program underlying aging.[4,5] In the mammalian brain, the course of aging parallels that of peripheral tissues, but additional mechanisms reflect the specificities of postmitotic and differentiated neurons,[2] which represent the major building blocks of the brain. At the cellular level, morphologic and stereologic studies reveal a decrease in neuron volumes, a small loss or no change in cell numbers,[6,7] and a progressive thinning of cortical thickness, affecting both gray and white matter.[8,9] The possibility to simultaneously monitor the function of many thousands of genes in postmortem samples has now revealed that aging of the human brain engages a specific and restricted set of biologic pathways,[10] hence refuting at the gene level the notion that aging is broad-ranging and nonspecific. McKinney and Sibille[11] summarize this information in this issue and discuss findings that suggest a framework for investigating brain aging and diseases, whereas the continuous lifelong trajectory of age-dependent gene changes greatly overlaps with similar changes observed in some neuropsychiatric disorders earlier in life. These findings provide molecular evidence for the specificity of mechanisms engaged during brain aging and for the well-known clinical and epidemiologic facts linking chronologic age and neuropsychiatric disorders of late life. Moving one step further, the authors suggest that this correlative overlap is consistent with a model where brain aging promotes biologic changes associated with diseases.

This putative model of age-by-disease biologic interactions is illustrated by two other reports in this issue. First, Dwivedi[12] provides a comprehensive review of the putative involvement of brain-derived neurotrophic factor (BDNF) in depression, including late-life depression. BDNF is a small peptide molecule secreted in the brain responsible for maintaining proper structure and function of multiple cell types in the brain, including neurons. Reduced BDNF levels have been implicated in some structural abnormalities of the brain observed in adult subjects with depression but also with other psychiatric disorders. Dwivedi[12] reviews the body of evidence that suggests similar BDNF-dependent mechanisms are engaged in the structural and functional changes in late-life depression. However, this continuum of pathologic changes is expected to interact with the "aging brain," providing a molecular and gene perspective both on similarities with adult life pathology (i.e., BDNF-dependent mechanisms) and specificities for the more complex biologic substrates of late-life geriatric depression.

In the next report, Douillard-Guilloux et al[13] shows the effects of reduced BDNF in midlife depression place numerous genes that are otherwise affected by age in control subjects on "accelerated" age trajectories. The authors further show that these accelerated age effects are not limited to genes that depend on BDNF and that the overall profile of age-dependent gene changes described earlier in this editorial is actually nudged in directions that would predict greater biologic age. This systematic correlation between age-dependent and depression-related changes, with greater effects in depressed subjects, demonstrates at the gene level that normal brain aging may indeed represent a biologic risk factor for depression, hence lending a critical biologic validity for the concept of an "older brain in depression."[14] Together, and illustrating the point mentioned earlier, this study demonstrates the opportunity provided by biologic changes occurring during normal aging in control elderly subjects to provide information on mechanisms underlying geriatric depression.

Consistent with the paradigm that deregulation of normal processes may underlie some functional deficits associated with symptom dimensions in geriatric population, Tatro et al.[15] identified, and report in this issue, changes in the expression of a member of a class of novel molecules that act as regulators of the function of other genes; These micro-RNA (miR) are small molecules of nucleic acid that are encoded in the genome and that, when expressed, regulate the function of multiple other genes, contributing to orchestrate cellular programs. The miR-138 member of this group is expressed in the hippocampus, a brain region that is critical for memory and that shows reduced volume with age. Tatro et al.[15] report that high expression and function of miR-138 correlates with sustained memory functions in old mice, suggesting that miR-138 may be involved in molecular and cellular mechanisms related to memory performance associated with healthy or successful cognitive aging. These findings may pave the way for targeted investigations in the human postmortem brain, based on the expected conservation of basic biologic mechanisms across species, and may thus provide novel molecular targets with relevance to the human geriatric population.

Finally, Pinnix et al.[16] tackle on the vexing situation that in several neurodegenerative disorders affecting the geriatric population, sets of disease-related genes and pathways have been identified, yet this knowledge has not been translated into a rational design of efficacious treatments. Specifically, the authors show that the pathway leading to the generation of amyloid proteins deposited in plaques implicated in the pathophysiology of Alzheimer disease may differ from that previously described. Through careful molecular analysis of enzymatic reactions, the authors demonstrate that the processing of the amyloid precursor protein yields smaller fragments than predicted (i.e., 50 amino acid product, rather than the expected 57 or 59 residues for the intracellular component). They further show that the yield of this newly characterized product is not only affected by a genetic variant of the processing enzyme identified in cases of familial Alzheimer disease but in a direction that suggests the need for a revision of current therapeutic approaches, or at least further investigations along directions provided by this report.

Echoing the title of this editorial, these reports highlight both the challenges of characterizing relevant biologic pathways within the vast complexity of the human and the opportunities provided by the unique biologic changes occurring in the aging brain. This suggests untapped opportunities provided by a detailed characterization of the aging brain for understanding basic aging mechanisms and their deregulations in the context of brain disorders. The establishment and strengthening of a culture supporting scientific endeavors toward a greater understanding of biologic mechanisms of normal and pathologic states require conceptual frameworks, goals, structures, and means. The National Institute of Mental Health organized a workshop to identify new research directions and goals (http://www.nimh.nih.gov/research-funding/scientific-meetings/2009/new-perspectives-in-the-translational-neuroscience-of-late-life-mental-disorders.shtml), and Evans[1] provide in this issue a commentary from the institute's point of view, highlighting consensus observations on the need to bridge the gap between basic studies and clinical correlates of the disease and to move beyond descriptive studies. Recent trends in translational studies of psychiatric and neurodegenerative disorders have demonstrated the strength of parallel investigations on multiple biologic scales and across species. The hope is that its application to the field of geriatric psychiatry and more broadly to the

investigation of brain- and age-based biologic mechanisms will provide significant information on novel leads for treatment and prevention. Importantly, the continuum of biologic phenomena along lifelong trajectories and the recruitment of "normal" pathways in disease states, as illustrated by several articles in this issue, indicate that the same biologic pathways are frequently engaged in normal brain aging and in disease states, including psychiatric disorders of late life, providing a compelling rationale for the simultaneous investigations of aging and brain disorders, with the goals of understanding disease mechanisms and uncover pathways to resiliency and successful aging.

The author has no disclosures. Support was provided by National Institute of Mental Health grants MH084060 and MH093723 (to ES). The funding agency had no role in decision to publish and preparation of the manuscript. The content is solely the responsibility of the author and does not necessarily represent the official views of the National Institute of Mental Health or the National Institutes of Health.

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